



## Angiosarcoma of the breast: a new therapeutic approach?



Raffaella Benevento\*, Francesco Carafa, Domenico Di Nardo, Gianluca Pellino, Antonia Letizia, Marianna Taddeo, Antonio Gambardella, Silvestro Canonico, Antonio Santoriello

Department of Medical, Surgical, Neurologic, Metabolic and Ageing Sciences, Second University of Naples, Naples, Italy

### ARTICLE INFO

#### Article history:

Received 24 March 2015

Accepted 2 June 2015

Available online 6 June 2015

#### Keywords:

Angiosarcoma

Electrochemotherapy

Breast

### ABSTRACT

**INTRODUCTION:** Angiosarcomas are highly malignant endothelial cell tumors with poor prognosis. These can be due to breast cancer itself or to subsequent therapeutic modalities. No evidence-based guidelines exist concerning the ideal treatment of angiosarcomas.

**PRESENTATION OF THE CASE:** We report the case of a 76-year-old woman who developed an exuberant and aggressive post radiation angiosarcoma of the breast and discuss different aspects of therapy for this disease. A total left mastectomy was performed, followed by a right mastectomy. The lesions into the chest wall, and multiple abdominal skin nodules were treated with local Electrochemotherapy (ECT) with intravenous bleomycin.

**DISCUSSION:** No evidence-based guidelines exist concerning the ideal treatment of angiosarcomas. Electrochemotherapy (ECT) is an efficient palliative treatment of cutaneous and subcutaneous tumor nodules. It consists of the combination of a cytotoxic drug and electroporation, using appropriate electrical parameters; destabilization of the membrane is reversible, ensuring a high survival of permeabilized cells and the delivery of non-permeant molecules inside the cell.

**CONCLUSION:** Due to the rarity of the disease, prospective studies concerning adjuvant or neoadjuvant therapy are limited and no evidence-based guidelines exist. The response to chemotherapy seems to be poor. Treatment with ECT in addition to systemic chemotherapy achieves a complete response in all the lesions and improving patient body image perception.

© 2015 The Authors. Published by Elsevier Ltd. on behalf of Surgical Associates Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### 1. Case report

In February 2011, we observed a 76-year-old woman with a painful, violet, multi-nodular mass occupying the entire left breast along with small nodules in right breast skin (Fig. 1). The lesion had rapidly enlarged. At the anamnesis she previously underwent breast-conservative surgery and axillary dissection for invasive ductal carcinoma of the left breast in 2003. Immunohistochemical analysis revealed estrogen and progesterone receptor positivity.

The tumor was classified as pT1 pN0 M0 G2 Stage I, according to the UICC–TNM classification. She received radiotherapy as follows: 50 Gy in 25 fractions of 200 cGy/daily with boost of 10 Gy in 5 fractions of 200 cGy/daily.

No adjuvant chemotherapy was given. She received adjuvant hormone therapy (Tamoxifene 20 mg daily for two years and Anastrozole for three years). The patient did not suffer from chronic lymphedema.

**Abbreviations:** ECT, electrochemotherapy; RIA, radiation induced angiosarcoma; RECIST, response evaluation criteria in solid tumors; ESOPE, European Standard Operating Procedures Of Electrochemotherapy.

\* Corresponding author at: Second University of Naples, Piazza Miraglia 2, 80138 Naples, Italy. Fax: +39 13142685466.

<http://dx.doi.org/10.1016/j.ijscr.2015.06.004>

2210-2612/© 2015 The Authors. Published by Elsevier Ltd. on behalf of Surgical Associates Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

In February 2007, the patient noticed a subcutaneous lesion of about 3 cm in diameter at the left breast. An excisional biopsy was performed. Histopathological examination revealed a vascular structure lined by atypical cells with hyperchromatic nuclei and eosinophilic cytoplasm.

Tumor cells were positive for CD34 and Vimentin and negative for SMA and CKP, indicating an endothelial origin. More than 90% of the cells in the solid component were positive for Ki67. The diagnosis of capillary-like grade-II angiosarcoma of the breast was made. No metastases were found at total body CT scan. Serum tumor marker levels were within normal limits. Adjuvant chemotherapy was not prescribed.

In February 2011, the cancer recurred replacing entirely the lower quadrants of the breast. It was violaceous, hemorrhagic and measured 12 × 9 cm. A total left mastectomy was performed, followed by repair of the skin defect using a dorsal skin graft. Microscopically, the lesion was composed of intricate vascular channels surrounding and invading the breast lobules. Numerous mitoses were observed. Immunohistochemistry showed CD31 and CD34 positivity. This was consistent with the diagnosis of capillary- and papillary-like grade-II angiosarcoma of the breast. A total body CT scan was repeated and showed no metastases.

The cancer was completely removed, but three months later the patient noticed a mass in her right breast with local relapse with

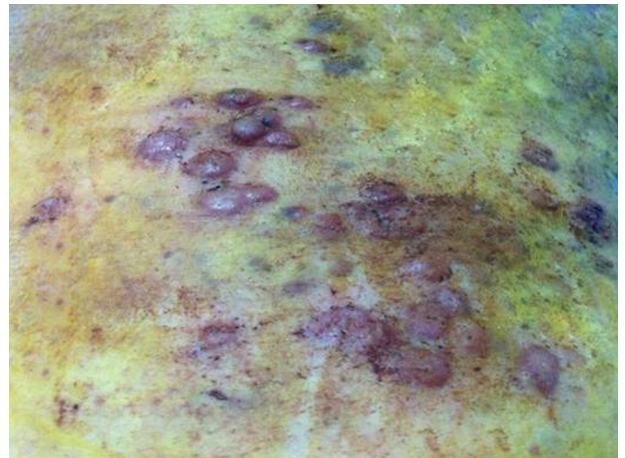


**Fig. 1.** Multi-nodular mass occupying the entire left breast.

multifocal nodes in her left chest wall. A right mastectomy was performed. The lesions into the chest wall were not amenable for surgery.

The left chest wall was treated with local ECT with intravenous bleomycin (Fig. 2). Treatment was performed according to the standard operating procedures for ECT (ESOPE – European Standard Operating Procedures of Electrochemotherapy) [9] under general anesthesia. Bleomycin 15000 IU/m<sup>2</sup> was injected intravenously. Pulses were delivered 8–30 min after injection [10]. Electric pulses were delivered using a square wave electroporator (IGEA, Carpi, Italy). The applied voltage was 1.0 kV/cm for needle electrodes, and pulses were applied at 5 kHz.

Six months later the patient developed multiple abdominal skin nodules not suitable for surgical treatment. Another treatment with ECT was performed (Fig. 3). Response rate was evaluated similarly to the response evaluation criteria in solid tumors (RECIST version 1.0) [11]. Overall, 51 lesion were treated at first and second thera-



**Fig. 3.** Multiple neoplastic abdominal skin nodules.

peutic session of ECT with median (range) diameter of 15 (10–25) mm. Considering all treated nodules (N=51), 51(100%) had complete response, as assessed at physical examination (Fig. 4).

No detectable metastatic disease was found. Adjuvant chemotherapy with Doxorubicine(40 mg/m<sup>2</sup>) was prescribed, repeated every 4 weeks for 6 cycles aiming to prevent distant recurrences. The patient is currently well with no recurrence 18 months after the operation.

**2. Discussion**

Angiosarcomas are rare malignant tumors which arise from endothelial cells lining vascular channels. Breast angiosarcomas can be either observed as primary neoplasms or, more commonly, in upper limb lymphedema as a result of breast conservative surgery and radiotherapy for breast carcinoma [1–10]. Radiation-induced angiosarcoma (RIA) was first reported in the literature in 1929 [11], and is a common form of angiosarcoma. The diagnostic criteria for RIA include: a previous history of radiotherapy, peak incidence between 5 and 10 years, development of sarcoma within a previous irradiated field, histology confirmation .RIAs are charac-



**Fig. 2.** Electrochemotherapy of multiple thoracic skin nodules, the needles are inserted into the lesion and electric pulses are delivered after intravenous injection of bleomycin.



**Fig. 4.** Complete response and no relapses is observed 18 months after Electrochemotherapy.

terized by their aggressive nature and most of them are high-grade tumors. The prognosis is poor and local recurrence rates reaches 70% after mastectomy [11–13]. RIAs often present as cutaneous or subcutaneous painless, flat or nodular, bluish or purplish lesion/s, similar to benign angiomas, small hematomas, or atypical telangiectasia [10].

Due to the rarity of the disease, prospective studies with regard to adjuvant therapy are limited and no evidence-based treatment guidelines exist [12,13]. Skin metastases from solid tumors behave in a similar fashion, irrespective of the tumor entity [14]. The lesions may be distressing for the patient, due to their visibility or symptoms such as weeping, bleeding, and pain.

ECT has emerged as an effective local treatment for patients with cutaneous and subcutaneous tumor nodules. It combines the effects of a cytotoxic intravenous drug and electroporation by means of electric fields, which temporarily increase the permeability of cell membrane allowing the direct diffusion of the drug within malignant cells [4,17–19].

ECT has recently been proposed as a novel, complementary therapeutic option for the control of superficial disease. This therapeutic approach is a feasible alternative in case of inoperable tumors, located in pre-irradiated areas and in areas resistant to chemotherapy [7,17,18,20]. Since recurrence and survival rate of angiosarcomas mainly depend on wide excision margins, safety histological margins of at least 5 cm are recommended, but may require extended excisions, which are not always possible. Due to the rarity of the disease, prospective studies concerning adjuvant or neoadjuvant therapy are limited and no evidence-based guidelines exist. The response to chemotherapy seems to be poor. However, anthracyclines are effective agents for soft tissue sarcomas and are mainly used as first-line therapy. In this case local treatment was combined with doxorubicin [15,16].

In our patient, presenting with unresectable and extended angiosarcomas, treatment with ECT in addition to systemic chemotherapy was likely to have significantly boosted the efficacy of the intravenous drug at the sites of angiosarcomas, achieving a complete response in all the lesions and improving patient body image perception. Neither symptomatic nor asymptomatic recurrences were observed at 18-months follow-up, suggesting that ECT is a promising tool in the palliative care of patients presenting with angiosarcomas after breast surgery.

#### Conflicts of interest

None.

#### Sources of funding

None.

#### Ethical approval

Our research is based on clinical notes of an individual patient and does not require research ethical approval.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy

of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### Author contribution

Nine authors have contributed to this study:

(1) All authors made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data.

(2) All authors participated in drafting the article or revising it critically for important intellectual content.

(3) All authors gave final approval of the version to be submitted.

#### Guarantor

MD Antonio Santoriello – Department of Medical, Surgical, Neurologic, Metabolic and Ageing Sciences, Second University of Naples, Naples, Italy.

#### References

- [1] H.B. Armah, U.N.M. Rao, A.V. Parwani, Primary angiosarcoma of the testis: report of a rare entity and review of the literature, *Diagn. Pathol.* 2 (2007) 23.
- [2] G. Hoffmann, I. Mylonas, Therapy of radiation-induced angiosarcoma of the breast in an elderly patient, *Arch. Gynecol. Obstet.* 287 (2013) 827–831.
- [3] L.M. Mir, Therapeutic perspectives of in vivo cell electropermeabilization, *Bioelectrochemistry* 53 (2000) 1–10, 8.
- [4] L.M. Mir, S. Orłowski, Mech. electrochemother, *Adv. Drug Del. Rev.* 35 (1999) 107–118.
- [5] R. Benevento, A. Santoriello, G. Perna, S. Canonico, Electrochemotherapy of cutaneous metastases from breast cancer in elderly patients: a preliminary report, *BMC Surg.* 12 (Suppl. (1)) (2012) S6.
- [6] R. Benevento, A. Vicidomini, et al., Electrochemotherapy of head and neck cancer in elderly patients: a preliminary report, *BMC Surg.* 1 (Suppl. (1)) (2013) A5.
- [7] M.S.G. Marty, J.R. Garbay, J. Gehl, et al., Electrochemotherapy: An easy, high and safe treatment of cutaneous and subcutaneous metastases: results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study, *Eur. J. Cancer Suppl.* 4 (2006) 3–13.
- [8] B. Mali, T. Jarm, M. Snoj, et al., Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis, *Eur. J. Surg. Oncol.* 39 (2013) 4–16.
- [9] P. Therasse, S.G. Arbuck, E.A. Eisenhauer, New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, National Institute of the United States, National Institute of Canada, *J. Natl. Inst. Cancer* 92 (2000) 205–216.
- [10] K.E. Torres, et al., Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer, *Ann. Surg. Oncol.* 20 (4) (2013) 1267–1274.
- [11] H.S. Martland, Occupational poisoning in manufacture of luminous watch dials, *JAMA* 92 (1929) 466–473.
- [12] K.H. Antman, J. Corson, J. Greenberger, R. Wilson, Multimodality therapy in the management of angiosarcoma of the breast, *Cancer* 20 (1982) 2000–2003.
- [13] R.M. Donnell, P.P. Rosen, P.H. Lieberman, R.J. Kaufman, S. Kay, D.W. Braun, D.W. Kinne, Angiosarcoma and other vascular tumors of the breast, *Am. J. Surg. Pathol.* 5 (1981) 629–642.
- [14] D. Nashed, F. Meiss, M. Braun-Falco, S. Reichenberger, Cutaneous metastases from internal malignancies, *Dermatol. Ther.* 23 (2010) 567–580.
- [15] S. Sleijfer, C. Seynaeve, J. Verweij, Using single-agent therapy in adult patients with advanced soft tissue sarcoma can still be considered standard care, *Oncologist* 10 (2005) 833–841.
- [16] M.A. Clark, C. Fisher, I. Judson, J.M. Thomas, Soft-tissue sarcomas in adults, *N. Engl. J. Med.* 353 (2005) 701–711.
- [17] M.P. Rols, J.M. Bachaud, P. Giraud, et al., Electrochemotherapy of cutaneous metastases in malignant melanoma, *Melanoma Res.* 10 (2000) 468–474.
- [18] R. Giardino, M. Fini, V. Bonazzi, et al., Electrochemotherapy: a novel approach to the treatment of metastatic nodules on the skin and subcutaneous tissues, *Biomed. Pharmacol.* 60 (2006) 458–462.
- [19] N. Solari, F. Spagnolo, E. Ponte, A. Quaglia, et al., Electrochemotherapy for the Management of Cutaneous and Subcutaneous Metastasis: a Series of 39 patients treated with palliative intent, *J. Surg. Oncol.* 109 (2014) 270–274.
- [20] G.L. Colombo, S. Di Matteo, L.M. Mir, Cost-effectiveness of Electrochemotherapy with the Cliniporator vs other methods for the control and treatment of cutaneous and subcutaneous tumors, *Ther. Clin. Risk Manag.* 4 (2008) 1–8.

#### Open Access

This article is published Open Access at [sciendo.com](http://sciendo.com). It is distributed under the [IJSCR Supplemental terms and conditions](#), which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.